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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/887,496	06/22/2001	Partha S. Banerjee	18025-1014	7707

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EXAMINER	
JIANG, SHAOJIA ANNA	
ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 01/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/887,496	BANERJEE ET AL.	
	Examiner	Art Unit	
	Shaojia A. Jiang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21,23-38,40-83,87-89,93 and 99-121* is/are pending in the application.

4a) Of the above claim(s) *65-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21, 23-38, 40-64, 69-83, 87-89, 93 and 99-121* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/27/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's amendment and response filed on September 27, 2004 wherein claims 1-21, 23-38, 40-64, 69-83, 87-89, 93 and 99-121 have been amended; claims 22 and 39 are cancelled.

Currently, claims 1-21, 23-38, 40-64, 65-68, 69-83, 87-89, 93 and 99-121 are pending in this application.

As recorded in the previous Office Action July 1, 2004, Claims 84-86, 90-92, and 94-98 are cancelled.

It is noted that claims 65-68 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Thus, these claims are not cancelled.

Claims 1-21, 23-38, 40-64, 69-83, 87-89, 93 and 99-121 as amended now are examined on the merits herein.

Applicant's declaration of Partha Banerjer (inventor), submitted September 27, 2004 under 37 CFR 1.132, is acknowledged and will be further discussed below.

Applicant's amendment filed on September 27, 2004 with respect to the rejection of claims 1-64, 69-83, 87-89, 93 and 99-121 made under 35 U.S.C. 112 second paragraph for the use of the indefinite recitations, i.e., "a subject", "a derivative", and "Britton-Robinson" and "Prideaux-Ward" in claims herein of record stated in the Office Action dated July 1, 2004 have been fully considered and found persuasive to remove

the rejection since these terms have been deleted from the claims. Therefore, the said rejection is withdrawn.

Applicant's amendment filed on September 27, 2004 with respect to the rejection of claims 87-89 made under 35 U.S.C. 112 first paragraph, for scope of enablement for "prevention" in claims herein of record stated in the Office Action dated July 1, 2004 have been fully considered and found persuasive to remove the rejection since the term has been deleted from the claims. Therefore, the said rejection is withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-21, 23-38, 40-64, 69-83, 87-89, 99-112 and 117-119 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carling et al. (US 5674860) in view of Hochrainner et al. (US 6150418), for same reasons of record stated in the Office Action dated July 1, 2004.

Carling et al. discloses a pharmaceutical composition comprising formoterol (free base) or formoterol fumarate salt in combination with the specific steroid anti-inflammatory agent, budesonide, in a pharmaceutically acceptable fluid such as a liquid

(see col.4 line 2), by inhalation from a nebulizer (see col.3 line 51) for the treatment of respiratory disorders such as asthma (see title and abstract, col.1 lines 10-15, 46-67). Carling et al. also discloses the effective amount of formoterol, 6-100 μg, preferred 6-48 μg (the instant claimed amount within the range of Carling et al.) in a pharmaceutical composition therein (see col.3 lines 44-45). Carling et al. also discloses that a pharmaceutical composition of the combination therein is formulated into a single dosage administration (see Example 1-3 at col.4). Carling et al. also discloses a kit or an article of manufacture comprising the same combination and a nebulizer (see col.3 line 8-10 and 50-52, claims 1-36). Carling et al. also discloses the employment of a tonicity adjusting agent herein such as salts of inorganic or organic salts, e.g., succinate, lactate (see col.3 lines 30-38) and adding oleic acid may improve the physical stability (see col.4 line 12-14).

Carling et al. does not expressly disclose the pharmaceutical composition comprising water, a polar solvent or a protic solvent, and Carling et al. does not expressly disclose that the concentration of formoterol in the aqueous solution is about 5 μg/ml- 2 mg/ml, and buffer providing particular pH value, and the ionic strength of the composition.

Hochrainner et al. discloses a pharmaceutical composition comprising formoterol particularly stable on storage with concentration 10 –500 mg/ml (see col.1 line 65-67; col.2 line 6-11), in **aqueous** ethanol of **water** and ethanol mixture (water and ethanol are well known polar and protic solvents, see col.2 lines 24-34), in the form of a solution or suspension for use in inhalers for nasal therapy, see abstract and claims 1-4 in

particular. Hochrainer et al. (6,150,418) further teaches that the pharmaceutical composition is such that it can be administered by inhalation using a suitable nebuliser, see col.4, lines 19-20 and col. 5, lines 33-41. Hochrainer et al. (6,150,418) further teaches that the pH range (preferably between 2.0-7.0 and most preferably between 4.5-5.5), the employment of inorganic acids such as phosphoric acids the employment of buffers in its composition, see in particular col.3, lines 35-40 and col.4 line 55 to col. 5, line 7; and adding inorganic and organic salts (see col.2 lines 56-64),. Hochrainer et al. (6,150,418) finally teaches that additional active ingredients such as **steroids** could be incorporated in its composition, see claim 19.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ water, a polar solvent or a protic solvent such as ethanol, and to adjust particular pH value by buffer, and to adjust the ionic strength of the composition by adding those inorganic and organic salts taught by Hochrainner et al. and Carling et al.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ water and ethanol and buffer solution in a inhalation composition, since water and ethanol and buffer solution are known to be used in the inhalation composition of Hochrainner et al. comprising formoterol in the aqueous solution with known pH ranges for the same inhalation therapy for suitable for stable storage.

Thus, employing water, ethanol and buffer solution, and adjusting particular pH value by buffer, and adjusting the ionic strength of the composition by adding those

inorganic and organic salts taught by Hochrainner et al. and Carling et al. are all deemed obvious since they are all within the knowledge and conventional skills in pharmaceutical science, involving merely routine skill in the art. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

Response to Argument

Applicant's argument sand declaration submitted under 37 CFR 1.132 filed September 27, 2004 with respect to the rejection made under 35 U.S.C. 103(a) as being unpatentable over the same prior art record in the previous Office Action July 1, 2004 have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art as further discussed below.

Applicant argues that Hochrainner et al. does not teach or suggest the claimed formoterol concentration in the aqueous solution is about 5 μg/ml- 2 mg/ml. However, as discussed above, Hochrainner et al. discloses a pharmaceutical composition comprising formoterol particularly stable on storage with concentration 10–500 mg/ml. It is also known that the effective amount of formoterol in a pharmaceutical composition, is 6-100 μg, preferred 6-48 μg according to Carling et al. Thus, optimization of known effective amounts of known agents in the aqueous solution to be administered according the disclosures of Hochrainner et al. and Carling et al., is considered well in the competence level of an ordinary skilled artisan and within the knowledge and conventional skills in pharmaceutical science. It has been held that it is within the skill

in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

Applicant's declaration under 37 CFR 1.132, is insufficient to overcome the rejection under 35 U.S.C. 103(a) for the following reasons. It has been held that any unexpected results submitted to rebut the prima facie case, the scope of the showing must be commensurate with the scope of the claims. *In re Coleman*, 205 USPQ 1172; *In re Greenfield*, 197 USPQ 227; *In re Lindener*, 173 USPQ 356; *In re Payne*, 203 USPQ 245.

In the instant case, the declaration fails to provide the concentrations of the testing formoterol aqueous solutions. Thus, it is unclear what the concentration of formoterol is in the testing. Therefore, the evidence in the declaration herein is not commensurate in scope with the claimed invention and does not demonstrate criticality of a claimed range of the concentration of formoterol in the claimed composition since See MPEP § 716.02(d).

Moreover, it is noted that the declaration provides no comparison with the closest prior art, e.g., the stability with the formoterol compositions of Hochrainner et al., in support of nonobviousness for the instant claimed invention over the prior art.

Thus, there is no clear and convincing evidence in the declaration for supporting the nonobviousness or unexpected results for the composition herein over the prior art. Therefore, the declaration is insufficient to rebut the prima facie case herein.

For the above stated reasons, said claims are properly rejected under 35 U.S.C. 103(a). Therefore, said rejection is adhered to.

Claims 1-21, 23-38, 40-64, 69-83, 87-89, 99-112 and 117-119 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blondino et al. (US 6004537) in view of Hochrainner et al. (US 6150418), for same reasons of record stated in the Office Action dated July 1, 2004.

Blondino et al. discloses a pharmaceutical composition comprising formoterol (free base) or formoterol fumarate salt in combination with the specific steroid anti-inflammatory agent, budesonide (see col.2 lines 9-25), in a pharmaceutically acceptable fluid such as a liquid, co-solvents of alcohols such as ethanol or isopropanol (see col.2 line 55-59), by inhalation from a nebulizer for treatment (see title and abstract, claims 1-30). Blondino et al. also discloses the effective amounts of formoterol, in amount 0.01-0.5% by weight in a pharmaceutical composition therein (see claim 1). Blondino et al. also discloses that the composition or formulation therein is stable under elevated temperatures, e.g., 45^0C (see col.2 lines 35-37). Blondino et al. also discloses that a pharmaceutical composition of the combination therein is formulated into a single dosage administration (see Example 1-4 at col.4). Blondino et al. also discloses a kit or an article of manufacture comprising the same combination and a inhaler (see col.3-4, claims 1-30).

Blondino et al. does not expressly disclose the pharmaceutical composition comprising water, and Blondino et al. does not expressly disclose that the concentration of formoterol in the aqueous solution is about 5 μg/ml- 2 mg/ml, and buffer providing particular pH value, and the ionic strength of the composition.

Hochrainner et al. discloses a pharmaceutical composition comprising formoterol particularly stable on storage with concentration 10 –500 mg/ml (see col.1 line 65-67; col.2 line 6-11), in aqueous ethanol of water and ethanol mixture (water and ethanol are well known polar and protic solvents, see col.2 lines 24-34), in the form of a solution or suspension for use in inhalers for nasal therapy, see abstract and claims 1-4 in particular. Hochrainer et al. (6,150,418) further teaches that the pharmaceutical composition is such that it can be administered by inhalation using a suitable nebuliser, see col.4, lines 19-20 and col. 5, lines 33-41. Hochrainer et al. (6,150,418) further teaches that the pH range (preferably between 2.0-7.0 and most preferably between 4.5-5.5), the employment of inorganic acids such as phosphoric acids the employment of buffers in its composition, see in particular col.3, lines 35-40 and col.4 line 55 to col. 5, line 7; and adding inorganic and organic salts (see col.2 lines 56-64),. Hochrainer et al. (6,150,418) finally teaches that additional active ingredients such as steroids could be incorporated in its composition, see claim 19.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ water, and to adjust particular pH value by buffer, and to adjust the ionic strength of the composition by adding those inorganic and organic salts taught by Hochrainner et al.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ water and ethanol and buffer solution in a inhalation composition, since water and ethanol and buffer solution are known to be used in the

inhalation composition of Hochrainner et al. comprising formoterol for the same inhalation therapy as Blondino et al.

Thus, employing water, ethanol and buffer solution, and adjusting particular pH value by buffer, and adjusting the ionic strength of the composition by adding those inorganic and organic salts taught by Hochrainner et al. are all deemed obvious since they are all within the knowledge and conventional skills in pharmaceutical science, involving merely routine skill in the art. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

Response to Argument

Applicant's same or substantially similar arguments and declaration submitted under 37 CFR 1.132 filed September 27, 2004, as the first 103(a) rejection, with respect to this rejection made under 35 U.S.C. 103(a) of record in the previous Office Action have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art as discussed above.

Claim 93 is rejected under 35 U.S.C. 103(a) as being unpatentable over Carling et al. (US 5674860) in view of Hochrainner et al. (US 6150418) further in view of PDR at pages 482, 535, 537, 2828 (of record), for same reasons of record stated in the Office Action dated July 1, 2004.

The same disclosures of Carling et al. (US 5674860) in view of Hochrainner et al. have been discussed in the 103(a) rejection set forth above.

Carling et al. and Hochrainner et al. do not expressly disclose further adding one or more agent recited in claim 93 herein to the composition of Carling et al. or Hochrainner et al.

PDR teaches that albuterol (beta2-adrenoreceptor agonist), accolate (leukotriene receptor antagonist) and Zyflo (5-lipoxygenase inhibitor) are all known to be effective in treating asthma.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ a third active such as those enumerated immediately above in a combination composition along with formoterol and budesonide.

One of ordinary skill in the art would have been motivated to employ a third active such as those enumerated immediately above in a combination composition along with formoterol and budesonide because all three actives are known to be useful in treating asthma. Combining two agents which are known to be useful to treat asthma individually into a single composition useful for the very snme purpose is prima facie obvious. See *In re Kerkhoven* 205 USPQ 1069.

Claims 113-116 and 120-121 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carling et al. (US 5674860) in view of Hochrainner et al. (US 6150418, of record) further in view of Hardman et al. (Goodman Gilman 's *The Pharmacological Basis of Therapeutics*,1996, page 665, of record) or Leckie et al (*Novel Therapy* Of COPD, abstract, Jan 2000, of record), for same reasons of record stated in the Office Action dated July 1, 2004.

The same disclosures of Carling et al. (US 5674860) in view of Hochrainner et al. have been discussed in the 103(a) rejection set forth above.

Carling et al. and Hochrainner et al. do not expressly disclose further adding an anticholinergic agent such as ipratropium bromide or tiotropium bromide to the composition of Carling et al. or Hochrainner et al.

Hardman et al. teaches that ipratropium bromide is an anticholinergic agent useful in treating asthma.

Leckie et al teaches that tiotropium is a known bronchodilator employed in treatment of asthma.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ a third active such as ipratropium bromide or tiotropium bromide in a combination composition along with formoterol and budesonide.

One of ordinary skill in the art would have been motivated to employ a third active such as ipratropium bromide or tiotropium bromide in a combination composition along with formoterol and budesonide because all three actives are known to be useful in treating asthma. Combining two agents which are known to be useful to treat asthma individually into a single composition useful for the very snme purpose is prima facie obvious. See *In re Kerkhoven* 205 USPQ 1069.

Applicant's same or substantially similar arguments and declaration submitted under 37 CFR 1.132 filed September 27, 2004, as discussed above, with respect to the above rejections made under 35 U.S.C. 103(a) of record in the previous Office Action

have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art as discussed above.

Further, the Examples 1-2 of the specification at pages 34-37 herein have been fully considered but are not deemed persuasive as to the nonobviousness and/or unexpected results of the claimed invention over the prior art, since Examples 1-2 provide no clear and convincing evidence of nonobviousness or unexpected results over the cited prior art, since there is no comparison to the same present.

For the above stated reasons, said claims are properly rejected under 35 U.S.C. 103(a). Therefore, said rejection is adhered to.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (571)272-0627. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

S. Anna Jiang, Ph.D.
Primary Examiner, AU 1617
December 28, 2004